REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1, 3-8 and 10-27 will be pending in the above-referenced patent application and are currently under examination. Claim 1 has been amended. Claim 27 is newly added. No new matter has been introduced with the foregoing amendment and newly added claim. Reconsideration is respectfully requested.

I. FORMALITIES

Support for the amendment and new claim is found throughout the application as originally filed. More particularly, support for the amendment to claim 1 is found, for example on page 16, lines 33-34. Support for new claim 27 is found, for example, in claim 1 as filed and on page 15, lines 32-34, bridging to page 16, at the top. As such, no new matter has been introduced and Applicants respectfully request that the amendment and new claim be entered.

Applicants previously submitted an Information Disclosure Statement on December 10, 2002. To date, Applicants have not received an initialed copy of Form PTO/SB/08B evidencing that the Examiner reviewed the same. Applicants respectfully request that the Examiner initial a copy of the previously submitted IDS and return the same to the undersigned representative.

II. THE INVENTION

The present invention relates to a novel and unobvious timed-release compression-coated formulation. The timed-release compression-coated formulation comprises a) a core tablet comprising a drug and a freely erodible filler, wherein the core tablet erodes approximately 40% to approximately 90% in the digestive tract, but still retains the shape of the compression-coated solid composition to a certain extent although it is being eroded; b) an outer layer, wherein the outer layer is made from a hydrogel-forming polymer substance, and a hydrophilic base, wherein the hydrogel-forming polymer substance has a viscosity-average molecular weight of 2,000,000 or higher and/or a viscosity in an aqueous 1% solution (25° C) of 1,000 cp or higher, and the hydrophilic base has a solubility such that the amount of water

needed to dissolve 1g of the hydrophilic base is 5 mL or less; and c) wherein the outer layer optionally contains another drug and the outer layer essentially does not contain the same drug as the core tablet drug.

III. REJECTION UNDER 35 U.S.C.§ 103

Claims 1, 3-8 and 11-25 were rejected as allegedly being obvious over Dandiker *et al.*, (U.S. Patent No. 5,425,950) in combination with Nakashima *et al.* (EP 0 661 045) in view of Taniguchi *et al.* (EP 0 709 386) both in further view of Wong *et al.* (U.S. Patent No. 5,391,381) and Kawata *et al.* (U.S. Patent No. 4,404,183). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure.
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> *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

Applicants assert that a *prima facie* case of obviousness has not been established as there is no suggestion or motivation to modify the cited references.

There is no Suggestion or Motivation to Modify the References

Applicants state that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Office Action has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of

ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The present invention relates to a timed-release compression-coated formulation. In the present invention, timed-release is achieved by the specific formulation of the core tablet and outer layer. The core tablet comprises an active ingredient and a freely erodible filler, and the outer layer comprises a hydrogel-forming polymer substance and hydrophilic base. Importantly, the core tablet is capable of approximately 40 to approximately 90% erosion. Surprisingly, Applicants have found that a percentage erosion of the core tablet of approximately 40 to approximately 90% is necessary for an ideal timed-release pharmaceutical preparation having high bioavailability (*see*, page 4, lines 16-24 of the specification).

Dandiker *et al.* disclose a compression coated tablet having an outer layer comprising a pH independent hydrophilic polymer. In operation, the outer layer is gradually removed by a combination of dissolution and erosion following administration and the inner layer or layers disintegrates rapidly once exposed within 30 minutes, although the Examples show the timed release data *in vitro*. Dandiker *et al.* set forth at col. 8, lines 13-19:

> [i]n a preferred aspect, the pulse release pharmaceutical compositions according to the invention provide a distinct pulse i.e. the release of active ingredient from the core after the initial predetermined time delay occurs over a relatively short time period (i.e. less than 30 minutes, e.g. less than 10 minutes) and there is no premature leakage of the active ingredient from the core.

Further, the viscosity of the pH independent hydrophilic polymers in the outer layer is preferably around 100 cps at 2% concentration in water. For example, col. 10, lines 7-16 sets forth:

> 3. Polymer solution viscosity. The rate at which the surface gel layer penetrates the interior of the dosage form is governed to some extent by the viscosity of the gel as well as its erosion. Release of the active ingredient can be controlled by selecting pH independent hydrophilic polymers with different chain lengths and differing viscosities. Higher viscosity polymers result in more delayed release of the active ingredient. **Polymers having a normal viscosity of around 100 cps at 2% concentration in water are preferred.** [Emphasis added].

As is presently taught and claimed, the outer layer in the present invention comprises a hydrogel forming polymer substance having a viscosity-average molecular weight of 2,000,000 or higher and/or a viscosity in an aqueous 1% solution (25° C) of 1,000 cps or higher and is thus, much different than the outer layer as taught by Dandiker *et al.* The present invention relates to the compression coated tablet having the specific outer layer and the specific core and the percentage erosion of the core tablet is approximately 40-90% in the digestive tract of the subject. Advantageously, the formulation of the present invention such as the whole tablet or the outer layer, still retain the shape of a compression-coated solid composition to a certain extent, although it is being eroded. The present tablet's characteristics enable an effective delivery of a drug to a specific site in the digestive tract and avoids reduction in bioavailability as a timed-release pharmaceutical preparation. Therefore, the invention of Dandiker *et al.* is totally different from the current invention.

Nakashima *et al.* do not supply the deficiencies of the primary reference. Nakashima *et al.* do not disclose an erodible core as is presently taught and claimed. Nakashima *et al.* disclose a sustained release formulation that comprises a drug, a hydrophilic base, and a hydrogel-forming polymer substance with drug release being possible in the upper digestive tract as well as the colon. Nakashima *et al.* do not teach or suggest a way to effectively deliver a high concentration of drug to a specific site in the digestive tract.

Again, with reference to enclosed Exhibit[1], the composition of the present invention is characterized by the following criteria: a) it absorbs the water in the upper digestive tract so that the outer layer all but completely gels; b) the water penetrates into the core tablet, and a solution state or suspension state is produced once the core tablet has been eroded prior to the outer layer disintegrating; c) the gelled outer layer is eroded as it moves to the lower digestive tract; and d) part of the outer layer is disintegrated or peeled, thus releasing the drug. Advantageously, ideal timed release of a drug can be achieved by this type of structure having a specific percentage erosion of the core tablet, even in the lower digestive tract with a low water content.

[1] The attached Exhibit was previously submitted in Applicants' response dated December 10, 2002.

In contrast, Nakashima *et al.* teach a hydrogel sustained-release pharmaceutical preparation made from drug, hydrophilic base, and hydrogel-forming polymer substance with which good drug release is possible in the upper digestive tract as well as the colon of the lower digestive tract (see, page 2, lines 16-20 of the specification). Applicants have discovered that the combination of a) adjusting the components in the core tablet, thereby controlling the percent erosion of the core tablet, and b) varying the mixture ratio of components in the outer layer is effective for achieving ideal timed release of a drug. For example, the addition of polyethylene glycol of high solubility in water to the core tablet is effective and that ***timed release*** can be adjusted by varying the mixture ratio of polyethylene glycol and polyethylene oxide in the outer layer. Examples in the specification teach various ratios of polyethylene glycol and polyethylene oxide suitable for preparing one formulation of the present invention. Nakashima *et al.* do not teach or suggest that the core tablet is capable of approximately 40 to approximately 90% erosion, which is necessary for an ideal timed-release pharmaceutical preparation having high bioavailability. Nakashima *et al.* teach the use of a hydrophilic base (*see*, page 6, lines 38-42 of Nakashima *et al.*) wherein the ratios are different than those of the present invention. Therefore, Nakashima *et al.* do not teach or suggest the timed-release compression coated formulations of the present invention. Furthermore, there is no suggestion or motivation to modify the references so that the core tablet is capable of approximately 40 to approximately 90% erosion. Prior to the advent of the present invention, it was not known that these percentages of erosion were necessary for the preparation of ideal timed-release pharmaceutical preparation having high bioavailability. Thus, one of skill in the art would not have been motivated to modify the teachings of Nakashima *et al.* to arrive at the present invention.

As the technology as taught by Dandiker *et al.* is totally different than the technology as taught by Nakashima *et al.*, there would be no motivation for a skilled artisan to combine these references. In fact, the hypothetical combination of the core tablet as taught by Dandiker *et al.* with the outer layer as taught by Nakashima *et al.* would still not teach the present invention, as the fillers, with the single exception of sucrose, are completely different from the a freely erodible filler in the core of the present invention.

The Examiner alleges that "[i]t can be concluded that any filler would erode to this percentage give enough time in the digestive tract." Applicants respectfully disagree.

Applicants have amended claim 1 by adding the phrase "but *still retains the shape of the compression-coated solid composition to a certain extent although it is being eroded.*" The focus of the claim is not the content of the "freely erodible filler" used in the core tablet, but the *percent erosion* of the core. In addition, new claim 27 has incorporated therein a method of measuring the percent erosion.

The teaching of Wong *et al.* relates to patterned drug delivery, including timed-release delivery. Although Wong *et al.* disclose tablet preparations including a polyethylene oxide and a red ferric oxide for coloring, the use of red and/or yellow ferric oxide for avoiding acceleration of the dissolution of a drug, as disclosed in the present invention, is ***not*** common in the art (*see*, page 18, lines 20-25 of the specification). Thus, one of skill in the art would ***not*** have been motivated by Wong *et al.* to include red and/or yellow ferric oxide in the compositions of Dandiker *et al.* as combined with Nakashima *et al.*, in order to stabilize the release properties of the drug.

Kawata *et al.* do not supplement the deficiencies of Dandiker *et al.*, Nakashima *et al.* and Wong *et al.* Kawata *et al.* disclose a sustained release pharmaceutical composition comprising (i) an amorphous drug such as nicardipine or a salt thereof, or indomethacine or a salt thereof, and the like, (ii) polyethylene oxide (PEO) and (iii) at least one basic substance such as HPMC and the like. Kawata *et al.* do not teach or suggest a core tablet capable of approximately 40 to approximately 90% erosion.

There is simply no suggestion or motivation to combine Kawata *et al.*, which achieves absorption enhancement and sustained release of a specific drug, with Dandiker *et al.*, Nakashima *et al.* and/or Wong *et al.* Moreover, there is no teaching or suggestion to effectively deliver a high concentration of drug to a specific site in the digestive tract. Therefore, a skilled person would not arrive at the present invention.

Taniguchi *et al.* do not supplement or add to the deficiencies of the other cited references. Taniguchi *et al.* teach a fused benzazepine derivative and pharmaceutical compositions containing the benzazepine derivative. Taniguchi *et al.* do not teach or suggest a

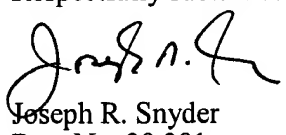
core tablet capable of approximately 40 to approximately 90% erosion as is presently claimed. Thus, Applicants respectfully request that the Examiner withdraw the rejection.

IV. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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Schematic description of gelling and drug release of TR in gastrointestinal tract